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NMR diffusion-ordered spectroscopy can explain differences in skin penetration enhancement between microemulsion formulations

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Abstract

Changing the formulation variables of microemulsion systems has a significant influence on the resulting transdermal enhancement effect. NMR diffusion-ordered spectroscopy (DOSY) can offer an extremely valuable tool to interpret the differences in the obtained fluxes based on variations in self-diffusions between the drug and its locus domain.

Key words: Microemulsions; NMR; Diffusion-ordered; Transdermal; Diffusion; Penetration enhancement

Microemulsion systems are usually considered as successful vehicles for transdermal drug delivery.[1] In part owing to the varied component composition, they usually offer excellent skin penetration enhancement. This is usually attributed to three key mechanisms; notably the hydration they impose to the stratum corneum due to their aqueous phase; the solubilizing power they impart to oil soluble drugs and finally the effect of the different surfactants and co-surfactants that are used in their production.[2,3] In this note, we introduce a new physical insight to interpret differences in penetration enhancement between microemulsion formulations based on studying the self-diffusion of a lipophilic drug *viz* testosterone relative to the diffusion of its residing oil phase. Such information can be readily obtained using diffusion ordered ^{1}H NMR spectroscopy (DOSY) and subsequently correlation of the values obtained with the testosterone fluxes through porcine skin.

Diffusion-ordered nuclear magnetic resonance (NMR) spectroscopy (DOSY) is a powerful technique that utilizes apparent translational diffusion coefficients in characterizing molecular species.[4] Several methods exist to extract diffusion coefficients from NMR data, the most visually appealing of which is a *pseudo* two dimensional spectrum where the conventional NMR is displayed in the direct dimension and the diffusion coefficient is depicted in the indirect one. Characteristic peaks for each component in the mixture may be traced. Recently, many applications have emerged utilizing this valuable technique in drug delivery using microemulsion systems such as: determination of the microemulsion type, detection of aggregates and determination of the drug locus inside the microemulsion.[5] Also, an attempt has been reported to correlate the self-diffusion coefficient of a certain drug; vinpocetine with its transdermal fluxes, although in this study the diffusion of the residing domain, though important, was neglected, leading to limited results interpretation.[6]

Transdermal fluxes of testosterone incorporated in microemulsion formulations were chosen along the dilution line L20 which starts at (% wt/wt) 20 oleic acid/40 Tween 20®/40 Transcutol® (having different water compositions from 5% to 23%) in the constructed phase diagram of the system oleic acid/Tween 20®/Transcutol®/water, were obtained from Hathout et al., 2010.[7] Diffusion-ordered spectroscopy (^{1}H) was performed in order to determine the self-diffusion coefficients of the drug and the oleic acid (the oil phase of the microemulsion and the drug locus).[7,8] The results were reported by Hathout and Woodman.[5]

Accordingly, testosterone transdermal steady state fluxes (J_{ss}) from the differently prepared microemulsion formulations were correlated with the self-diffusion of testosterone ($D_{testosterone}$) in these microemulsions normalized with the diffusion of oleic acid ($D_{oleic\ acid}$); its locus phase in the microemulsion (Figure 1). A very good correlation ($r = 0.90$) was obtained. It was observed that increasing the water content of the microemulsions had a lower effect on testosterone diffusion compared to oleic acid; the

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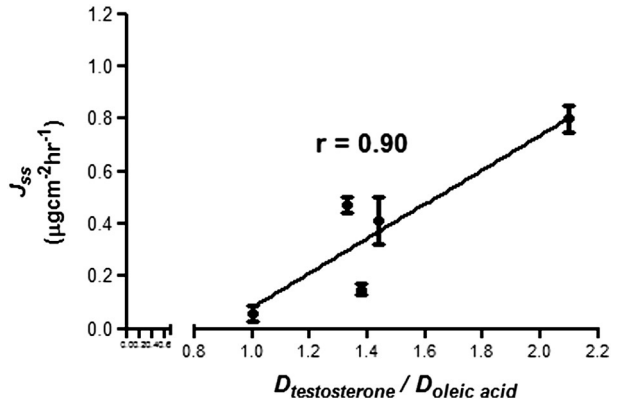

Figure 1. Correlation between testosterone transdermal fluxes across porcine skin and its normalized self-diffusion in the microemulsion system oleic acid/Tween 20®/Transcutol®/water.

ratio $D_{testosterone}/D_{oleic\ acid}$ increased by increasing the microemulsion water percentage. In other words, the difference in mobility between the drug and its domain was increased. Interestingly, this was also accompanied by an increase in testosterone fluxes through the porcine skin. The flux through the skin (drug penetration) usually follows the diffusion (or partitioning) of testosterone to the outer surface of the skin (i.e. A > B > C). The slower of these consecutive steps determines the final rate. In concentrated microemulsions, the diffusion step (A > B) is slower than the penetration step therefore it becomes the rate-limiting one. It may be expected that, after a certain dilution with water the diffusion becomes faster and the second step becomes rate-limiting. However, in the current study increasing the water content further caused the disappearance of the microemulsion area[7] so the former case prevailed. We assume that increasing the water content relatively constrains the diffusion of the oily phase (where lipophilic drugs such as testosterone reside) and generates relative diffusion differences between the drug and its domain. This enhances the potential for the drug to leave its locus and partition to the aqueous phase and the skin surface thereafter or to directly diffuse to the skin surface if the oily domain comes into direct contact with it. Consequently, we encourage potential researchers working on transdermal delivery using microemulsion systems to consider similar correlations in interpreting the microemulsion's composition effects on skin penetration or permeation. Using NMR diffusiometry; a simple but a very effective method for quality control (using low field NMR) and for research (using high field NMR) is a new idea in the field of transdermal delivery research.

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Graphical Abstract

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Transdermal flux of testosterone is correlated with the normalized self-diffusion of the drug relative to its locus self-diffusion.

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